Final Results: A Dose Escalation Phase 1 Study of ARQ 197, a Selective c-MET Inhibitor, in Patients with Metastatic Solid Tumors

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BACKGROUND

- c-MET is a receptor tyrosine kinase implicated in tumor cell migration, invasiveness, and proliferation.
- c-MET is dysregulated in a broad spectrum of human cancers.
- ARQ 197 is a selective, non-ATP competitive inhibitor of c-MET.
- ARQ 197 demonstrates efficacy in a range of human cell lines and xenograft models, including human lung, prostate, colon, pancreas, and breast cancers.
- Selective inhibitors of c-MET are being investigated in clinical trials and show promising efficacy in a variety of solid tumors.

METHODS

Study Design:
- Phase 1 dose escalation study in patients with metastatic solid tumors

Objectives
- Evaluate the safety of ARQ 197
- Determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of ARQ 197
- Evaluate the pharmacokinetic (PK) profile of ARQ 197
- Evaluate the preliminary anti-tumor activity of ARQ 197
- Evaluate preliminary signals of efficacy

Drug Administration and Dosing Schedule
- Two dosing schedules were explored
  - Schedule A (initial schedule): oral twice daily (BID) for 2 weeks followed by 1 week off
  - Schedule B (introduced after initial safety established in Schedule A): oral BID continuous dosing
- A treatment cycle was defined as 3 weeks for both dosing schedules

Dose escalation
- Followed an accelerated titration design initially
- Followed a modified traditional escalation design (3+3 patients) once Grade 2 toxicity was observed
- Intra-patient dose escalation was allowed once the safety of a higher dose level was established
- Expansion cohort was enrolled at the initial RP2D of 120 mg BID continuous dosing (Schedule B)
- Additional patients were enrolled and treated at 360 mg BID with a continuous dosing schedule, which was determined to be the MTD in another Phase 1 clinical trial

Pharmacokinetics and pharmacodynamics
- Two sets of PK samples were collected from all patients on study Days 1 and 14 of Cycle 1
- When available, archival tissue was collected and evaluated for total c-MET, phospho-c-MET (p-c-MET), phospho-FAK (p-FAK), and hepatocyte growth factor (HGF)

Tumor Measurement and Assessment
- Tumors were measured at baseline, weeks 6 and 12, and every 9 weeks thereafter until disease progression
- Responses were assessed according to RECIST 1.0

RESULTS

- As of 1 May 2009, 74 patients have been treated with ARQ 197 in this trial, with 13 cohorts of patients being assessed at doses ranging from 10–360 mg BID. The demographics of these patients are reported in Table 1.
  - A total of 37 patients received initial doses between 10 and 180 mg BID on Schedule A, with a further 37 patients receiving initial doses between 120 and 360 mg BID on Scedule B (Table 2).
- Adverse events (AEs) considered to be related to study drug occurred in 30 (40.5%) patients.
  - The most common drug-related AEs were fatigue (16.2%), nausea (12.2%), vomiting (6.8%), and diarrhea (5.4%) (Table 3).
  - Drug-related serious AEs (SAEs) occurred in 4 patients (Table 4).
- No dose-limiting toxicity (DLT) was observed at any dose < 360 mg BID. DLTs were reported in 2 patients at 360 mg BID.
  - One patient experienced neutropenia, thrombocytopenia, and leucopenia which resolved in 9 days, with treatment continuing.
  - One patient experienced dehydration and vomiting which resolved in 6 days when treatment was discontinued.
- No MTD was identified in this study.
- Although the primary objective of the study was not to determine efficacy, 61 patients were evaluable for assessment of anti-tumor activity (an evaluable patient is defined as a patient with evaluable post-treatment tumor measurements for RECIST 1.0 evaluation).
  - 3 patients with neuroendocrine, prostate, and testicular cancers achieved a partial response (PR), for a response rate of 4.9% in the evaluable population (Table 5)
  - 38 patients had a best response of SD and 20 had PD (Table 6)
  - Disease control (complete response + PR + SD) was achieved in 67.2% of the evaluable patients
  - The median duration of therapy was 6.5 weeks (range; 1-119 weeks)
  - Duration of drug exposure by tumor type by patient is presented in Figure 1.
- Under the dosing regimen of 360 mg BID, the mean C_{max} (n=7) was 1516 ng/mL and the mean $AUC_{(0-8hour)}$ was 8506 hour*ng/mL. Based on in vitro IC_{50} data for c-MET, all patients remained above the minimum inhibitory concentration of 0.3 µM for 8 hours or longer.
- Patient 8 with prostate cancer showed high expressions of total c-MET, phospho-c-MET, phospho-FAK, and HGF at baseline (Figure 2).

Figure 1. Weeks on ARQ 197 treatment by tumor type and patient

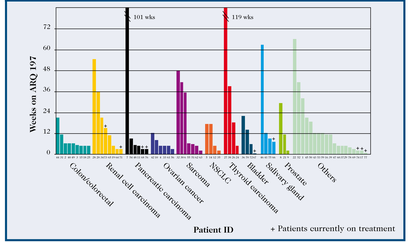


Table 1. Patient baseline demographics (N=74)

Age, years	
Median (range)	61.5 (16.8–86.7)
Sex, n (%)	
Male	43 (58.1)
Female	31 (41.9)
Race, n (%)	
Caucasian	60 (81.1)
Black	5 (6.8)
Hispanic	4 (5.4)
Asian	4 (5.4)
Other	1 (1.4)
Karnofsky Performance Status (KPS), n (%)*	
100%	11 (13.7)
90%	36 (49.3)
80%	27 (37.0)
No. of prior therapies, median (range)	
Surgery	2.0 (0, 19)
Radiotherapy	0.5 (0, 6)
Chemotherapy	4.0 (0, 15)

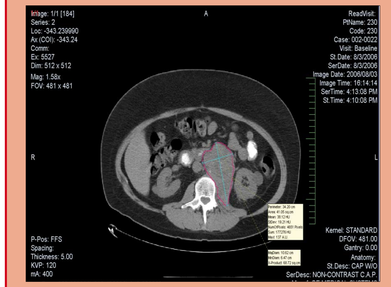
* one patient is missing KPS data.

Table 2. Initial ARQ 197 dosing cohorts

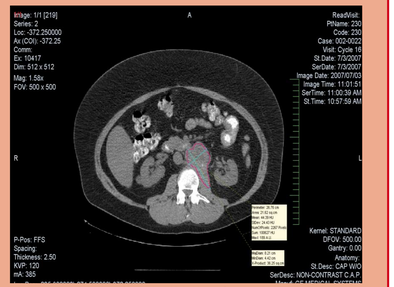
Schedule	Initial Cohort (mg BID)	No. of patients (N=74)	%
A	10	1	1.4
	20	1	1.4
	30	3	4.1
	40	4	5.4
	50	3	4.1
	70	5	6.8
	90	5	6.8
	120	7	9.5
	150	5	6.8
	180	3	4.1
B	120	21	28.4
	150	3	4.1
	360	13	17.6

Figure 3. Patient 022's cancer history and CT scans

- Patient was a 49-year-old Caucasian male with testicular cancer (60% seminoma, 35% endodermal sinus tumor [yolk sac tumor], and 5% choriocarcinoma) diagnosed in 1997.
- The patient underwent surgery with curative intent in 1997, followed by multiple systemic treatment regimens, including platinum/etoposide/bleomycin, platinum/ifosfamide/etoposide, taxol/ifosfamide/cisplatin, sunitinib, and vinblastine.
- Following 47 weeks of treatment with ARQ 197, the patient had a confirmed PR lasting 18 weeks.
- In addition to the radiographic response, the patient's alpha-fetoprotein level decreased from 57.0 ng/mL at baseline to 25.4 ng/mL following 9 weeks of treatment.
- The patient's Karnofsky Performance Status improved from 80% at baseline to 90% after 15 weeks on treatment, where it remained for the duration of treatment.



03 August 2006



03 July 2007 (32.9% reduction)

Figure 2. Pre-treatment biomarker expressions in patient 008 with prostate cancer (best response: PR)

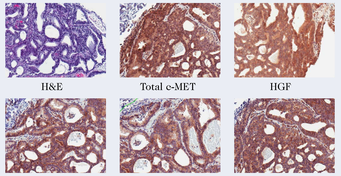


Table 3. Number (%) of patients with most common (>5%) drug-related adverse events (AEs)

		No. patients (%) (N=74)	
MedDRA Preferred Term	**Total**	**10–180 mg BID (N=61)**	**360 mg BID (N=13)**
Patients with ≥ 1 drug-related AEs	30 (40.5)	25 (41.0)	5 (38.5)
Fatigue	12 (16.2)	11 (18.0)	1 (7.7)
Nausea	9 (12.2)	8 (13.1)	1 (7.7)
Vomiting	5 (6.8)	3 (4.9)	2 (15.4)
Diarrhea	4 (5.4)	4 (6.6)	0

Table 4. Number (%) of patients with drug-related serious adverse events (SAEs)

MedDRA Preferred Term	No. of patients (%) (N=74)	Dose (mg BID) at time of SAE
Patients with ≥ 1 drug-related SAE	4 (5.4)	
Blood and lymphatic system disorders	1 (1.4)	
Leucopenia	1 (1.4)	360
Neutropenia	1 (1.4)	360
Thrombocytopenia	1 (1.4)	360
Metabolism and nutrition disorders	1 (1.4)	
Dehydration	1 (1.4)	360
Gastrointestinal disorders	1 (1.4)	
Abdominal pain	1 (1.4)	120
Nausea	2 (2.7)	120, 360
Vomiting	2 (2.7)	120, 360
Hepatobiliary disorders	1 (1.4)	
Hepatic failure	1 (1.4)	120

Table 5. Patients with a partial response (PR) to treatment

ID	Tumor type	Dose (mg BID)	Treatment duration (weeks)	Time to PR	Duration of PR (weeks)
001	Neuroendocrine	10 escalated to 50	32	32	5
008	Prostate	40 escalated to 50 then to 70	29	5	6
022	Testicular	90 escalated to 120 (continuous)	66	47	18

Table 6. Best tumor response per RECIST 1.0 criteria by tumor type (N=61. Evaluable population)

Tumor type	N (%)	PR	SD	PD
Colon/colorectal	8 (13.1%)	0	2	6
Renal cell carcinoma	7 (11.5%)	0	6	1
Sarcoma	7 (11.5%)	0	4	3
Pancreatic cancer	3 (4.9%)	0	2	1
Ovarian cancer	5 (8.2%)	0	3	2
NSCLC	3 (4.9%)	0	2	1
Thyroid carcinoma	4 (6.6%)	0	4	0
Bladder	3 (4.9%)	0	3	0
Salivary	4 (6.6%)	0	3	1
Prostate cancer	1 (1.6%)	1	0	0
Others	16 (26.2%)	2	9	5
Total	61 (100%)	3	38	20

PR, partial response; PD, progressive disease; SD, stable disease.

CONCLUSIONS

- ARQ 197 has a favorable safety profile up to the dose of 360 mg BID.
- In the prostate cancer responder with archival tissue available, pre-treatment biomarker analyses showed elevated levels of the phospho-c-MET target and the HGF ligand, and their downstream substrate phospho-FAK.
- 67.2% of evaluable patients experienced disease control with ARQ 197, suggesting preliminary evidence of anti-cancer activity.
- ARQ 197 is a promising targeted anti-cancer treatment that warrants further investigation for clinical efficacy.
- Phase 2 clinical trials evaluating the anti-tumor activity of ARQ 197 in several tumor types are ongoing.

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